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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,522	05/08/2006	Steven M. Leventer	1818400181OUS	5139

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DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE, SUITE 2000
PHILADELPHIA, PA 19103-6996

EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DBRIPDocket@dbr.com
penelope.mongelluzzo@dbr.com

Office Action Summary	Application No.	Applicant(s)	
	10/578,522	LEVENTER ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-9 and 17-21 are pending currently and they are the subject of this Office Action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 17 September 2010 has been entered.

Applicants' arguments, filed on 17 September 2010 have been fully considered and are deemed to be persuasive regarding the previous rejections. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn.

Upon reconsideration of the pending claims, as presented, the following new rejections are applied. They constitute the complete set of rejections being applied to the instant application presently.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103 (a) that form the basis for the rejections under this section made in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejection set forth in the Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 17-21 are rejected under 35 U.S.C. 102(a) as being obvious in view of Ito, Chihiro, et al., "Pharmacological Studies of Tofiospam," *Res. Lab Pharmacol.*, Mochida Pharm. Co., Ltd., Tokyo, Japan (1981) in view of U.S. Patent No. 6,093,740 [hereinafter referred to as "Jirousek et al"].

Applicant argues that there is nothing in Ito et al that relates to the observed increase in pain threshold to any effect involving inflammation and further, there is nothing in Ito et al that teaches or suggests the use of tofiospam for the treatment of an inflammatory disorder of the epithelium and no dose information is given by Ito et al either and finally, the present invention is distinguishable over the prior art in that the prior art does not meet the terminology "substantially free of the corresponding (S)-enantiomers" as defined by Applicants' specification.

The teachings of Jirousek et al from this Office's Action of 28 April 2009 are incorporated herein by reference in their entirety. Additionally, the teachings of Ito et al, as outlined in the Office's Actions of 31 October 2007, 04 September 2008, and 28 April 2009 are incorporated herein by reference in their entirety. Ito, et al teach the pharmacological effects of tofiospam, both *in vivo* and *in vitro*, to include elevation in pain thresholds when administered orally (See Abstract). Additionally, it is important to note that the claims of the instant invention suggest the same compound as the Ito et al reference.

Further, as a matter of law, compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds

differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). *See also In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers *prima facie* obvious). The necessary motivation to make the claimed compound, and thus the prima facie case of obviousness, arises from the reasonable expectation that compounds similar in structure will have similar properties. In re Gyurik, 596 F.2d 1012, 1018 (CCPA 1979).

Daiichi Sankyo v. Apotex, 84 USPQ 1285 (Fed. Cir. 2007): reference taught that ciprofloxacin lacked ototoxicity when used to treat middle ear infections; another reference taught that ofloxacin and ciprofloxacin are both gyrase inhibitors and belong to the same family of compounds; court held that it would have been obvious to one of ordinary skill in the art to substitute ofloxacin for ciprofloxacin in the treatment of othopathy with a predictable expectation of successful treatment due to the compounds' structural and functional similarities (note: this a post-KSR c ase)

Optimization of the acid addition salt formulation for an active pharmaceutical ingredient is obvious where the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art suggests the particular anion used to form the salt. Pfizer v. Apotex, 82 USPQ2d 1321, 1336 (Fed. Cir. 2007). Moreover, one skilled in the art would expect various anions to provide salts having a range of properties, some of which

would be superior, and some of which would be inferior, to any given salt. Id. 1338. (note: this is a post KSR case)

As legal authority the examiner cites In re Adamson, 125 USPQ 233 (CCPA 1960). The case sets forth the requirements of patentability with regard to stereoisomers as follows:

> 1) The existence of a racemate is, in and of itself, sufficient to render obvious any individual stereoisomers contained within; no express suggestion of isomer separation is needed. See p. 235, ¶ 1.
>
> 2) One skilled in the art expects that individual stereoisomers will differ significantly physiological/pharmacologic activity and toxicity, because living systems are chiral and thus preferentially process certain stereochemical configurations over others. See p. 234, third full paragraph, and p. 235, fifth full paragraph.

As such, the disclosure in Ito et al brings the instant claims within the purview of the previously disclosed art.

Ito et al disclose the administration of tofiospam as a treatment of edema formation, noting an oral administration of 160 mg/kg having the effect of suppressing spontaneous locomotion and administration of more than 300 mg/kg significantly inhibiting acetic acid-induced stretching. Additionally, there was a significant increase observed in the pain threshold when in excess of 1000 mg/kg was administered (Page 587, Nos. 1 and 2 of Summary). Ito et al also discloses the intravenous administration of 3 mg/kg of tofiospam having a hypotensive effect and also exerting a relaxing action of isolated smooth muscular organs and antagonistic action to acetylcholine, histamine, barium chloride and nicotine (Page 587, Nos. 3 and 4 of Summary). In giving the claims their broadest reasonable interpretation, the "about language" in Applicants' claims brings them within the purview of the dosages prescribed by Ito et al.

Jirousek et al disclose the administration of a compound to treat dermal edema and that the same may be administered orally and/or topically (Abstract and Col. 8, lines 49-67). Jirousek et al also disclose that dermal edema is characterized by an accumulation of fluid extractive from vascular space into dermal interstitial space which could form blister formation (Col. 7, lines 6-10) and that the same is a major feature of a number of skin disorders including certain bacterial and viral infections, allergic skins disorders and dermatitis (Col. 7, lines 4-23).

One of ordinary skill in the art would be motivated to modify the teachings in Ito et al by the teachings in Jirousek et al to arrive at the instant invention, because of the overlapping subject matter shared by both references. Notably, both references are directed in one matter or another to the treatment of an inflammatory disorder.

In light of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat an individual inflicted with an inflammatory disorder of epithelial tissue by administering to them tofiospam.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia R. Hughes/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614